Abstract

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Title of diploma thesis: *In vitro* study of antiproliferative effects of selected topoisomerase II inhibitors.

Anthracycline antibiotics (such as doxorubicin or daunorubicin) are antineoplastics which act as the topoisomerase II poisons. They stabilize a reaction intermediate in which DNA strands are cut and covalently linked to tyrosine residues of topoisomerase II, eventually impeding DNA resealing. Failure of relaxing the supercoiled DNA results in block of DNA replication and transcription. Doxorubicin is used for the treatment of solid tumours as well as haematologic malignancies, while daunorubicin can be used to treat specific types of leukaemia. Unfortunately, cardiotoxicity represents serious side effect of these drugs. Therefore, combinations of anthracyclines with cardioprotective agent dexrazoxane are sometimes used. The proposed mechanism of dexrazoxane cardioprotective action is chelation of the iron ions which decrease the production of reactive oxygen species. Dexrazoxane is also a catalytic inhibitor of the topoisomerase II and there are doubts, whether it may compromise the antitumour effectiveness of the anthracyclines.

The aim of our work was therefore to assess the effects of different topoisomerase II catalytic inhibitors (dexrazoxane, sobuzoxane and merbarone) on the cytotoxicity of athracycline antibiotics against proliferating cancer cells.

In this study, the promyelocytic leukaemia HL-60 cell line was used. The cells were treated with variable concentration of selected compounds or their combinations for 72 hours. The MTT test was used for the measurement of the cellular viability. This test is based on bioreduction of the thiazolyl blue tetrazolium bromide by viable cells. To assess apoptosis induction, activities of caspases 3, 8 and 9 were determined using specific chemiluminescence substrates.

Our results indicate that the combinations of anthracycline antibiotics with catalytic topoisomerase II inhibitors do not compromise their antiproliferative activities. At least an additive effect of the two compounds was observed and the synergistic effect was observed for some concentration combinations.